RESPONSE UNDER 37 C.F.R. §1.129(a)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Carol A. Westbrook

Serial No.: 07/784,222

Filed: October 28, 1991

For: METHODS AND COMPOSITIONS FOR THE DETECTION OF CHROMOSOMAL ABERRATIONS

Examiner: D. Rees

Group Art Unit: 1807

Atty. Dkt: ARCD:010/PAR

CERTIFICATE OF MAILING
37 C.F.R. 1.8

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August 19, 1997
Date

David L. Parker

FIRST SUBMISSION UNDER 37 C.F.R. §1.129(a) AND
RESPONSE TO OFFICE ACTION MAILED FEBRUARY 25, 1997

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a preliminary response, under transitional practice, to the Final and Advisory Actions accompanying applicant's request for entry of amendments "after final" under 37 C.F.R. §1.129(a). A final Office Action was mailed February 25, 1997, an amendment and request for

reconsideration under 37 C.F.R. § 1.116 was mailed on April 24, 1997 and an Advisory Action was mailed on May 20, 1997. No notice of appeal or appeal brief have been filed in the present case. A petition and fee for a three month extension of time, to August 25, 1997, is filed herewith. The present submission is thus being timely submitted prior to mailing of any appeal brief, in consideration of the petition for a three month extension.

Pursuant to Rule 129, Applicant respectfully requests that the finality of the subject Office Action be withdrawn, and that the following amendments and arguments be considered in the captioned patent application in accordance with 37 C.F.R. § 1.129(a). Should any additional fees under 37 C.F.R. § 1.16-1.21 be deemed necessary, the Assistant Commissioner is authorized to deduct said fees from Arnold, White & Durkee Deposit Acct. No. 01-2508/ARCD:010/PAR.

Applicant is requesting entry of amendments previously denied entry by the examiner. This "transitional after final" practice is proper in this case given that the filing date is October 28, 1991 and since Applicant submits herewith the requisite fee under 37 C.F.R. § 1.17(r).

AMENDMENTS

In the Claims:

Please cancel without prejudice ~~or disclaimer~~ claim 4.

Please amend the claims as follows:

1. (Twice amended) A composition comprising a ~~pair~~ of probes for detecting a chromosomal aberration which juxtaposes the BCR and ABL genes, said pair of probes comprising

RESPONSE TO OFFICE ACTION

I. Status of the Claims

Claim 4 has been canceled without prejudice or disclaimer. Claims 1, 11, 12, 15, 16, 22, 23 and 31 have been amended. New claim 34 has been added. Claims 1-3 and 5-34 are presently in the case and are presented for reconsideration. A copy of the pending claims is attached hereto as Exhibit A. The specific grounds for rejection and applicant's response thereto are set out in detail below.

The applicant would like to thank examiner Rees for her many helpful and constructive comments during the course of this prosecution. Her statements concerning what might constitute allowable subject matter were particularly helpful. Claims 1, 11, 12, 15, 16, 22, 23 and 31 have been amended in accordance with the examiner's suggestions to more clearly point out the subject matter of the invention.

II. Support for the Claims

New claim 34 merely tracks the language of amended claim 1, in the form of a kit. Support for claim 34 may be found in the specification at least at page 2, line 37 through page 4, line 9; page 6, line 34 through page 7, line 16; page 8, line 15 through page 10, line 21; page 11, line 8 through page 14, line 25; page 16, line 1 through page 43, line 19 and Figure 2.

Support for the amended claim 1 is found in the specification at least on page 2, line 37 through page 4, line 9; page 6, line 34 through page 7, line 16; page 8, line 15 through page 10, line 21; page 11, line 8 through page 14, line 25; page 16, line 1 through page 43, line 19 and Figure 2.

The use of paired probes to detect the BCR:ABL translocation is described at page 10, lines 8-17 and page 13, lines 20-22. The recitation that at least part of the hybridization sites for the first and second probes be brought within approximately 800 kb of each other is supported in the specification at page 8, lines 18-21 and page 10, lines 19-21. The use of probes specifically designed to bind to regions of the BCR and ABL genes on either side of the translocation breakpoint is supported by the specification at page 13, lines 4-12, page 14, lines 15-25 and Figure 2.

III. Rejection of Claims 1-22, 29, 31-33 Under 35 U.S.C § 112, First Paragraph.

The examiner has rejected claims 1-22, 29 and 31-33 under 35 U.S.C § 112, first paragraph as lacking an enabling disclosure. The examiner raises a number of distinct points in finding a lack of enablement. Each of these concerns is addressed below.

The examiner states that "the specification, while being enabling for compositions comprising probes of defined sequence, does not reasonably provide enablement for probes recited by the function of hybridizing to ABL nucleic acid flanking sequence or BCR nucleic acid flanking sequence." (Office Action mailed 2/25/97, pages 2-3) The Office Action points out that "flanking sequences" could be interpreted as being limited to ABL and BCR nucleic acids, or could be interpreted to encompass sequences quite distant from ABL and BCR. (*Id.* at 4) The Action states, however, that the breakpoints for the BCR/ABL translocation, as well as the sequences of both ABL and BCR, were known in the art at the time the invention was made. (*Id.* at 5)

Applicant has amended claim 1 eliminate the phrase "flanking sequence." The amended claim 1 tracks the language suggested by Examiner Rees in a facsimile communication dated June 9, 1997, except that the language has been slightly modified to clarify that a hybridization site for the first probe and a hybridization site for the second probe are brought within approximately 800 kb of each other. The requested amendment has been phrased in this manner to address the possibility of others "designing around" the claimed invention by using extremely large probes that have hybridization sites partially within 800 kb of each other and partially outside of 800 kb of each other. As noted in the specification at page 10, lines 5-7, the instant invention contemplates probes of up to 200 kb in size. Such large probes could encompass correspondingly large hybridization sites.

As shown in Figure 2, the binding site for the c-H-abl probe disclosed in the instant application encompasses the last exon of the ABL gene. Similarly, Figure 2 shows that the binding site for the PEM12 probe disclosed in the instant application encompasses the 5' region of the major breakpoint cluster region, while the binding site for the MSB-1 probe encompasses exon I of BCR. Thus, the probes MSB-1 and PEM12 were designed to bind to the BCR gene on one side of the translocation breakpoint and the probe c-H-abl was designed to bind to the ABL gene on the other side of the translocation breakpoint.

Amended claim 11 recites a first probe having the property of being capable of hybridizing to at least a portion of the last exon of the ABL gene and a second probe capable of hybridizing to at least a portion of exon I of the BCR gene. Such probes would have the utility disclosed in the specification of detecting both the p190 and p210 fusion genes. The amendment is supported at

least by pages 10, 20, 22-24, 31-32 and Figure 2 of the specification. The MSB-1 and c-H-ras probes disclosed in the specification have the properties of hybridizing to at least portions of exon I of BCR and the last exon of ABL, as recited in claim 11.

The Action states that the specification is enabling for compositions comprising probes of defined sequence. (Office Action mailed Feb. 25, 1997, page 2) Applicant submits that the defining features of the probes are clearly recited in claims 1-3 and 5-34. Applicant further submits that, given the enabling nature of the specification for probes of defined sequence and the Action's statement that the sequences of BCR and ABL were known in the art, any skilled practitioner of the art could have determined, without undue experimentation, additional probes within the ABL and BCR sequences having the same disclosed utility of binding on either side of the translocation site, thereby allowing detection of the recombinant p190 or p210 fusion genes.

Applicant submits that the claims as amended provide a clear and concise written description of the invention. Applicant further submits that it was well within the ability of the skilled artisan to make and use the invention, given the state of the art at the time of the invention, the information provided within the specification and the clarity of the amended claims. Applicant therefore requests reconsideration of the claims and withdrawal of the rejection.

IV. Rejection of Claims 1-33 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-33 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. Applicant wishes to thank the examiner for her many helpful suggestions in this section of the Office Action. The examiner's specific objections are addressed below.

Applicant notes the claim 1 has been amended to eliminate the recitations of "an ABL nucleic acid flanking sequence" and a "BCR nucleic acid flanking sequence." The amended claim 1 recites probes that are capable of specifically hybridizing to a part of the ABL gene and a part of the BCR gene located on either side of a chromosomal aberration, said genes juxtaposed by the chromosomal aberration. Given the statement in the Action that the sequences of the BCR and ABL genes and the location of the translocation breakpoint were known in the art, the metes and bounds of this claim would be clear to the skilled artisan.

Claim 12 has been amended to omit the word "No."

The word "designated" has been removed from amended claims 15, 16 and 31. With regard to deposit of the probes under the terms of the Budapest Treaty, applicant assures the Patent Office that an acceptable deposit will be made on or before the date of payment of the issue fee in accordance with 37 C.F.R. § 1.809.

Claim 23 has been amended to remove the words "3' end of the ABL gene." The amended claim 23 recites a probe capable of hybridizing to at least a part of the last exon of the ABL gene. Applicant submits that the last exon of the ABL gene is clearly described in the specification.

As stated above, the word "designated" has been removed from amended claims 15, 16 and 31.

Applicant submits that it is fundamental patent law that claims are to be read in light of the specification and both are to be read with a view to ascertaining the invention. *United States v.*

Adams, 383 U.S. 39, 15 L. Ed.2d 572, 86 S. Ct. 708 (1966). The standard for § 112, second paragraph is whether one skilled in the art would be able to determine what subject matter is claimed. *Hybritech, Inc. vs. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986).

Applicant submits that reading the specification and claims together, the skilled artisan would be able to determine the subject matter of claims 1-3 and 5-34, as amended. The Action states that the location of the ABL:BCR translocation breakpoints, as well as the sequences of BCR and ABL, were known in the art at the time the invention was made. (Office Action mailed Feb. 25, 1997, page 5)

Amended claim 1 clearly recites those portions of the Philadelphia chromosome within the scope of the instant invention. Amended claim 1 recites a pair of probes, one specifically hybridizing with a portion of the ABL gene on one side of a chromosomal aberration and the other specifically hybridizing with a portion of the BCR gene on the other side of the chromosomal aberration, wherein a hybridization site for the first probe is brought within 800 kb of a hybridization site for the second probe by the chromosomal aberration. Since the Action states that the sequences of BCR and ABL and the location of the translocation breakpoint were known in the art, the skilled artisan would have been well able to determine the metes and bounds of the invention.

Applicant submits that the claims as amended particularly point out and distinctly claim the subject matter of the invention. Applicant submits that the amended claim 1 and all dependent claims particularly point out and distinctly claim the regions adjacent to the BCR:ABL

translocation sites within the subject matter of the invention. Reconsideration and withdrawal of the rejection is respectfully requested.

V. Rejection of Claims 1, 4, 8, 9, 11, 12, 14, 17-20, 22, 23, 30, 31 Under 35 U.S.C. § 102

The Action has rejected claims 1, 4, 8, 9, 11, 12, 14, 17-20, 22, 23, 30 and 31 under 35 U.S.C. § 102(a) as being anticipated by Stephenson *et al.* (1987). Stephenson *et al.* recite synthetic oligonucleotides useful in the diagnosis of CML, including probes complementary to the bcr-abl splice site.

Applicant submits that the reference by Stephenson *et al.* does not anticipate the claims of the instant invention. Rejection under 35 U.S.C. § 102 is improper unless each and every element of the claimed invention is present in a single prior art reference. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986). Applicant submits that the instant invention incorporates several elements that are missing from the reference by Stephenson *et al.* cited by the examiner.

One element of the instant invention is that the probes of the claimed composition must be utilized in pairs. Independent claim 1 recites a pair of probes, one binding on either side of the translocation breakpoint. This element is incorporated into dependent claims 2, 8, 9, 11, 12, 14, 17-20 and 31.

Nowhere does Stephenson *et al.* teach the utilization of probes in pairs. Nowhere does Stephenson *et al.* even suggest the use of their probes in pairs, nor would they have had any motivation to use their probes in pairs. In contrast, the instant invention could only work with

paired probes. Without a first and a second probe, one binding on either side of the translocation breakpoint, there would be no way to detect CML or ALL in accordance with the present invention. The requirement of using probes in pairs forms an additional element of the present invention, not taught by Stephenson *et al.*

Independently of the above-mentioned element, several of the amended claims are outside the scope of Stephenson *et al.* Amended claim 11 specifies a first probe capable of binding to at least a portion of the last exon of ABL and second probe capable of binding to at least a portion of BCR exon I. The Office Action states on page 7 that Stephenson *et al.* teach synthetic oligonucleotides complementary to a sequence in BCR exon 2 and a sequence in ABL exon 2. Thus, both exon I of BCR and the last exon of ABL would be outside the teachings of this reference.

In claim 22, the word "region" has been deleted. The claim now recites a genetic probe capable of hybridizing to the first exon of the BCR gene. For the reasons cited above, this is outside the teachings of Stephenson *et al.*

Similarly, claim 23 has been amended to delete the phrase "the 3' end of the ABL gene." The claim now recites a probe capable of hybridizing to at least a part of the last exon of the ABL gene. Again, this is beyond the teachings of Stephenson *et al.*

Claim 30 incorporates the recitations of amended claims 22 and 23. Since claims 22 and 23 are outside the scope of Stephenson *et al.*, claim 30 is also outside the scope of this reference.

For these reasons, applicant submits that the instant invention does not "read on" Stephenson *et al.* and rejection of the claims under 35 U.S.C. § 102 is improper. Reconsideration of the claims is respectfully requested.

IV. Rejection of Claims 2 and 29 Under 35 U.S.C. § 103

The Action has rejected claims 2 and 29 under 35 U.S.C. § 103 as being unpatentable over Stephenson *et al.* (1987). The Action states that "Stephenson *et al.* meets all of the limitations of the claims except for the teaching of a labeled probe or the teaching that the probes are provided in a kit." (Office Action mailed 2/25/97 at page 8) Applicant notes that claims 3, 5, 6, 7, 10, 13, 15, 16, 21 and 24-28 were not rejected under either § 102 or § 103 and are therefore considered by the Examiner to be free of the prior art.

Rejection of claims under § 103 is improper unless the prior art reference (or references when combined) teach or suggest all the claim limitations. *In re* Vaeck, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). Applicant submits that the claims of the instant invention contain elements that are neither taught nor suggested by any prior art reference, either alone or in combination, as discussed below.

It is significant that the MSB-1 probe of the instant invention binds to exon I of the BCR gene, while the c-H-abl probe binds to the last ABL exon. Thus, they are capable of detecting <u>all</u> BCR-ABL fusions that could predispose to CML or ALL. There is no equivalency between the probes taught by Stephenson *et al.* and the MSB-1 and c-H-ras probes taught in the instant invention. According to the Action, the probes of Stephenson *et al.* are complementary to BCR

exon 2 and ABL exon 2. Thus, they are not capable of hybridizing with BCR exon I or the last ABL exon. The reference of Stephenson *et al.* could not have made either the MSB-1 or c-H-ras probes or methods utilizing these probes obvious, since Stephenson *et al.* did not teach how to make or use these probes, nor did they teach any method for obtaining these probes. Stephenson *et al.* do not even suggest that it would be desirable to obtain probes such as MSB-1 or c-H-ras.

There is no teaching in Stephenson *et al.* that would provide a skilled practitioner of the art with either the guidance or motivation to make and use the instant invention. There is no suggestion in this references as to how a practitioner would obtain the MSB-1 or c-H-ras probes or their equivalents. Therefore, this reference cannot have provided a practitioner with the motivation to develop the instant invention. In the absence of such motivation, the cited reference only provides a mere "invitation to experiment" that cannot support an obviousness rejection. *In re O'Farrell*, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988).

The amended form of claim 1 even more clearly points out the distinction between the instant invention and the recitations of Stephenson *et al.*, as it includes the element of paired probes that is missing from Stephenson *et al.* Dependent claim 2 includes all the limitations of claim 1, and thus also includes the element of paired probes missing from Stephenson *et al.* Applicant further notes that claim 29 incorporates the limitations of amended claims 22 and 23. These claims recite probes capable of hybridizing to the first exon of the BCR gene and at least a part of the last exon of the ABL gene. Therefore, the probes taught by Stephenson *et al.* do not meet all the limitations of claim 29 besides the kit format, as the probes of Stephenson *et al.* are not capable of binding to either the first exon of BCR or last exon of ABL. (Office Action mailed 2/25/97 at page

7, last paragraph) Therefore, rejection of claims 2 and 29 under 35 U.S.C. § 103 is not proper and applicant requests that the rejection be withdrawn.

Applicant respectfully traverses the assertion that "the art provides the motivation to provide compositions of the recited probes for the purposes of Southern analysis of chromosomal aberrations...." (Office Action mailed 2/25/97, page 10) A feature of the instant invention is the use of probes in pairs. Applicant submits that the art at the time of the instant invention provided no motivation for the use of paired probes, particularly where each member of the pair was differentially labeled. At the time of the instant invention, the art generally taught two means of using probes for Southern analysis. The primer extension method provided a labeled single oligonucleotide for hybridization with target nucleic acids, while the nick translation method provided a multiplicity of labeled oligonucleotides. Neither of these techniques would have resulted in a pair of labeled probes, binding on opposite sides of a chromosomal aberration. Applicant further submits that for the purpose of Southern blotting, there is no reason and no motivation to use paired probes.

For the reasons stated above, applicant respectfully submits that the examiner has failed to establish a *prima facie* case for obviousness. Applicant requests that the rejected claims be reconsidered in light of this argument.

VII. Summary and Conclusion

In light of the foregoing comments, applicant submits that all pending claims are in condition for allowance and solicits an early indication to that effect. Should Examiner Rees feel that further discussion of any of the issues is merited, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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